(21)Application number: 11-006162 (22)Date of filing: 13.01.1999

(71)Applicant: DAINIPPON PHARMACEUT CO LTD
(72)Inventor: SHIRAI HISAMI, SOGAWA KIYOMI, OGASAWARA KAZUYOSHI, AZUMA YUTAKA, NAKAMURA YASUHIKO

(30)Priority
Priority number: 10 17947 Priority date: 14.01.1998 Priority country: JP

(54) DISINTEGRATING TABLET IN ORAL CAVITY AND PRODUCTION THEREOF

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a disintegrating tablet in oral cavity showing a good disintegrating property in the oral cavity, and having a sufficient strength, and to provide a method for producing the large amount of the above tablet simply by not using a special equipment.
SOLUTION: This method for producing a disintegrating tablet in oral cavity, comprises the following processes (a), (b) and (c), and blending a medicine before a granulation or before a tablet formation. (a) a process for dissolving at least one kind of a saccharide having a high solubility to water (e.g.; xylitol), and at least one kind of a water soluble binder (e.g.; a polyvinylpyrrolidone), (b) a process for mixing at least one kind of an excipient (e.g.; mannitol), granulating, drying and then tabletting under a low compression, and (c) a process for aging tablets obtained by the above process (b).

CLAIMS

[Claim(s)]
[Claim 1]It consists of the following steps (a), (b), and (c), Sugars with high solubility to manufacturing method:(a) water of a chewable tablet, wherein a granulation front stirrup mixes a drug before tableting in a process (b) at least A process of a kind and a water-soluble binding material which dissolves a kind in a water independent or water, and alcohols at least, (b) A process which mixes a kind of excipient at least in a solution obtained at the above-mentioned process (a), and is tableted with low pressure after drying, a granulation and, a process of aging a tablet obtained at the (c) above-mentioned process (b).
[Claim 2]The manufacturing method according to claim 1 whose aging in a process (c) is what warms a tablet obtained at a process (b) for several 10 seconds - for several days at temperature exceeding a room temperature.
[Claim 3]The manufacturing method according to claim 1 or 2 whose solubility of sugars used at a process (a) is about 40g - about 250g to 100 ml of about 25 ** water.

[Claim 4]The manufacturing method according to claim 1 or 2 whose sugars used at a process (a) are the things of erythritol, xylitol, sorbitol, glucose, and a shook sirloin chosen from a kind at least.
[Claim 5]The manufacturing method according to any one of claims 1 to 4 whose water-soluble binding material is a thing of a polyvinyl pyrrolidone, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, and water-soluble gelatin chosen from a kind at least.
[Claim 6]The manufacturing method according to any one of claims 1 to 5 whose solvent used at a process (a) is water.
[Claim 7]The manufacturing method according to any one of claims 1 to 6 whose loadings of sugars used at a process (a) are about 0.5 of a tablet - 10 % of the weight of abbreviation.
[Claim 8]The manufacturing method according to any one of claims 1 to 7 whose loadings of a water-soluble binding material are about 0.5 of a tablet - 5 % of the weight of abbreviation.
[Claim 9]aging in a process (c) -- warming -- they are conditions -- the warming -- the manufacturing method according to any one of claims 1 to 8 temperature is lower than softening temperature of a water-soluble binding material used at a process (a), and is not less than about 40 ** in temperature and whose time of aging is for [about 1 minute] - about 24 hours.
[Claim 10]It consists of the following steps (a), (b), and (c), Sugars with high solubility to chewable tablet:(a) water manufactured with a manufacturing method, wherein a granulation front stirrup mixes a drug before tableting in a process (b) at least A process of a kind and a water-soluble binding material in which a kind is dissolved with a water independent or water, and alcohols at least, (b) A process which mixes a kind of excipient at least in a solution obtained at the above-mentioned process (a), and is tableted with low pressure after drying, a granulation and, a process of aging a tablet obtained at the (c) above-mentioned process (b).
[Claim 11]It consists of the following steps (a), (b), and (c), Sugars with high solubility to chewable tablet:(a) water manufactured with a manufacturing method, wherein a granulation front stirrup mixes a drug before tableting in a process (b) at least A process of a kind and a water-soluble binding material in which a kind is dissolved with a water independent or water, and alcohols at least, (b) A process which mixes a kind of excipient at least in a solution obtained at the above-mentioned process (a), warms a tablet obtained at a process tableted with low pressure after drying, a granulation and, and the (c) above-mentioned process (b) at temperature further exceeding a room temperature, and is aged for several 10 seconds - for several days.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the chewable tablet manufactured by the manufacturing method and said manufacturing method of the tablet (a "chewable tablet" is called hereafter) which collapses easily within the mouth.
[0002]
[Description of the Prior Art]Although an aging society is greeted and the pharmaceutical preparation of the gestalt which is easy to take for elderly people is demanded, under the present circumstances, many of oral pharmaceutical preparation is still usual tablets and capsules, and

administration is not necessarily easy for elderly people. In these usual pharmaceutical preparation, it is also common for administration to be difficult also for a child or the difficult patient of a deglutition. There is a problem of adhering in the problem of the handling in the time of opening or the mouth, and it can be satisfied with neither powder medicine nor a granule for elderly people, and a child and the difficult patient of a deglutition. Even when he has no water, it can take and some pharmaceutical preparation is already tried about the tablet with easy handling, in order to solve such a problem.

[0003]In JP,S62-50445,B, at the blister of PTP (press through package) A drug, Pour in the suspension of sugars and a gelling agent, and freeze-drying removes moisture, it is indicated by the method of fabricating a tablet within a blister, and in WO No. 12769 [93 to] gazette. The suspension of a drug, mannitol, and agar is poured into the blister of PTP, reduced pressure drying removes moisture, and the method of fabricating a tablet within a blister is indicated.

[0004]In the patent No. 2650493 gazette (WO93-15724). The fast-melting lock which dissolves promptly within the mouth manufactured by compressing the humid granulation which makes a subject the sugars corned with water, and drying is indicated, and the manufacturing method of the chewable tablet which tablets the mixture which contains in JP,H5-271054,A the moisture which is a grade in which a particle surface carries out humidity is indicated.

Generally these manufacturing methods are known as a wet manufacturing process.

[0005]In JP,H8-291051,A and JP,H9-48726,A. Sugars are made into a subject, and after carrying out compression molding of the granular material which added the water-soluble binding material with low pressure, the method of placing and carrying out humidity of the tablet under humidification, drying this, and manufacturing a chewable tablet is indicated (the "humidifying method" may be called hereafter).

[0006]In the patent No. 2640570 gazette (WO93-13758). After carrying out low-pressure compression molding of the granular material which added water-soluble colliquative binding materials, such as poly ERIREN glycol, The manufacturing method of the tablet which intensity increased is indicated by by making it dissolve at a temperature higher than the melting point of a water-soluble colliquative binding material, and subsequently solidifying a water-soluble colliquative binding material (a "heating fusion method" may be called hereafter).

[0007]In JP,H9-316006,A, the solubility solid preparations in the mouth which have improved cool feeling are indicated by containing erythritol and a little solid organic acid.

[0008]The Schar form matrix in the state where the cotton candy-like thing amorphous as a special method was cut in WO No. 34290 [95 to] gazette on the other hand is prepared, This is made into a fluid good grain, the manufacturing method subsequently used as a tablet is indicated, and the tablet manufactured using said Schar form matrix is indicated to WO No. 34293 [95 to] gazette, and JP,H8-38138,A.

[0009]

[Problem(s) to be Solved by the Invention]Although collapse is a quick tablet in the porosity produced by how the intensity of a tablet is raised pursuing, each tablet explained above making sugars etc. a subject, and maintaining porosity, All have problems, such as complicatedness of manufacture, and a cost aspect, and the manufacturing method which was excellent in the comprehensive target as a manufacturing method of a chewable tablet is demanded.

[0010]For example, the tablet obtained by said JP,S62-50445,B by the method of a description has low tablet strength, and when extruding from PTP, there is a fault which a trouble produces.

Machinery is that it is complicated and newly needed, and a manufacturing process is not advantageous at a cost aspect, either. On the other hand, although tablet strength has improved in the method given in WO No. 12769 [93 to] gazette, like JP,S62-50445,B, a manufacturing process is complicated and is not advantageous at a cost aspect.

[0011]The granular material which became wet with the method by said wet manufacturing process adheres to a mortar or a pestle easily at the time of tableting, a certain device is needed also for carrying out constant feeding of the humid powder to a mortar further, and it is unsuitable for continuous tableting. Therefore, in order to solve these problems, improvement of the tableting machine itself may be needed (refer to JP,H8-19589,A and JP,H8-19590,A).

[0012]The process of humidifying a tablet in said humidifying method in addition to the process of manufacturing the usual tablet is suitable for neither a drug unstable to humidity, nor the drug in which deliquescence is shown with high humidity required. There is a not suitable problem in a drug unstable with heat, or a drug with bad combination nature with a water-soluble colliquative binding material in said heating fusion method.

[0013]

[Means for Solving the Problem]This invention persons dissolve sugars with high solubility to water, and a water-soluble binding material in water, as a result of inquiring that this conventional problem should be solved, and using this by the conventional wet granulation. It can take out from PTP easily, and has the intensity which does not make handling produce a problem, and a manufacturing method excellent in an economic target which can manufacture an outstanding chewable tablet which collapses promptly within the mouth was found out.

[0014]According to this invention, it consists of the following steps (a), (b), and (c), Sugars with high solubility to manufacturing method:(a) water of a chewable tablet, wherein a granulation front stirrup mixes a drug before tableting in a process (b) at least A process of a kind and a water-soluble binding material in which a kind is dissolved with a water independent or water, and alcohols at least, (b) A kind of excipient is mixed at least in a solution obtained at the above-mentioned process (a), and a granulation and after drying, a process tableted with low pressure, a process of aging a tablet obtained at the (c) above-mentioned process (b), and a chewable tablet manufactured by the above-mentioned manufacturing method are provided.

[0015]Below, a term of this Description is explained.

[0016]In this Description, with "sugars with high solubility to water." Sugars which have such character relatively in what is generally called sugars are meant, and that whose solubility (measurement of solubility is later mentioned hereafter since "solubility" is only called) to 100 ml of purified water in about 25 ** is about 40g - about 250g is mentioned. As an example of these sugars ("sugars used by this invention" may be called hereafter), Although glucose of monosaccharide, xylose [the 12th edition of solubility about 125g;Merck Index and 10220 (1996) references], xylitol of sugar-alcohol, sorbitol, erythritol, and a shook sirloin (white soft sugar) of disaccharide are mentioned, Erythritol, xylitol, and a shook sirloin are preferred. Although these sugars are independent, or two or more sorts can be mixed, it can use and it is usually contained among a tablet abbreviation 0.1- about 20% of the weight, about 0.5 - 10 % of the weight of abbreviation are preferred.

[0017]Therefore, in this Description, mannitol and lactose do not correspond to "sugars with high solubility to water", as shown in after-mentioned working example, but they are treated as sugars other than sugars used by this invention, for example. [in / low / for solubility / this

invention]

[0018]With sugars used by this invention A water independent or water, and alcohols. [binding material / water-soluble] What can make it dissolve in (for example, ethanol), and demonstrates desired unity as a result is meant, For example, a polyvinyl pyrrolidone is preferred although a polyvinyl pyrrolidone, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, gum arabic, water-soluble gelatin, etc. are mentioned. It can be independent, or two or more sorts can be mixed, and these water-soluble binding materials can be used. loadings of these water-soluble binding materials -- the inside of a tablet -- usually -- about 0.1- about 20% of the weight of a range -- desirable -- about 0.5- it is chosen out of about 5% of the weight of a range.

[0019]Although cornstarch is water solubility and it is generally used as a binding material, a dissolution rate to water is slow, therefore collapse delay of a tablet formed cannot use it as said water-soluble binding material in this invention remarkably.

[0020]Although sugars other than sugars used for this invention, for example, mannitol, lactose, and mannose can usually be used as an excipient, sugars used for this invention can also be used.

[0021]If it is a drug which can carry out [****]-izing with usual wet granulation or fluidized bed granulation method, anything can be used for a chewable tablet of this invention, but mosapride citrate, alacepril, brotizolam, a hydrochloride of berberine or tannate, and loperamide hydrochloride are mentioned, for example. Although the granulation front stirrup can mix a drug in a process (b) at any stage before tableting, mixing before a granulation is preferred. Per tablet, content of a drug is about 0.01 - 20 % of the weight of abbreviation, and is usually about 0.1 - 10 % of the weight of abbreviation preferably.

[0022]In a chewable tablet of this invention, sweetners and an aromatic for improving a feeling of administration if needed may be added. Lubricant required for the usual pharmaceutical preparation process and disintegrator may be added.

[0023]Tableting in low pressure in the above-mentioned process (b) is performed by about 20 - about 300 kg/cm^2, and is usually preferably performed by about 50 - about 200 kg/cm^2.

[0024]a tablet obtained at the above-mentioned process (b) -- the usual aging (preferably room temperature of not less than about 15 **), i.e., a room temperature, -- several hours - a divisor, although it becomes a chewable tablet which has desired intensity by neglecting it during a day, A tablet obtained at the above-mentioned process (b) can be warmed at temperature exceeding a room temperature, and a process aged for several 10 seconds - for several days can also be added positively.

[0025]Although carried out temperature which "aging" means making pharmaceutical preparation physical properties, such as a tablet, into a stationary state, and usually allows aging to stand at a room temperature, or exceeds a room temperature, and by warming above about 30 ** preferably, It is a temperature lower than softening temperature of a water-soluble binding material used by this invention, and it is still more preferred to carry out at temperature of not less than about 40 **, and it is much more preferred to carry out at about 40 ** - about 80 **. Not only a method shown in this Description but processing which makes pharmaceutical preparation physical properties, such as a tablet, a stationary state by other methods is included in aging in this Description.

[0026]"Softening temperature" means temperature to which it will become soft if solid material is heated, and modification becomes easy, a polyvinyl pyrrolidone is specifically about 150 **, and hydroxypropylcellulose is about 130 **.

[0027]
[Embodiment of the Invention]As a desirable manufacturing method of the chewable tablet of this invention, the following gestalten are mentioned, for example.
[0028]A manufacturing method of a chewable tablet, wherein it consists of following steps (a'), (b'), and (c') and a granulation front stirrup mixes a drug before tableting in a process (b') : (a') Erythritol, The sugars 0.5 [about] chosen from a kind at least - 10 % of the weight of abbreviation and the polyvinyl pyrrolidone of xylitol, sorbitol, glucose, and a shook sirloin, The process in which the water-soluble binding material 0.5 [about] chosen from a kind at least - 5 % of the weight of abbreviation of pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, and water-soluble gelatin are dissolved by a water independent or water, and ethanol, (b') A kind of excipient is mixed at least in the solution obtained at the above-mentioned process (a'), The process of being lower than the softening temperature of the water-soluble binding material used at a process (a'), and aging the tablet obtained at the process (c') tableted with the low pressure of about 50 - about 200 kg/cm^2, and the above-mentioned process (b') after drying, a granulation and at the temperature of not less than about 40 ** for about 1 more minute to about 24 hours.
[0029]Below, the manufacturing method of this invention is explained in more detail.
[0030]A water independent or if needed, add alcohols and the sugars and the water-soluble binding material which are used for this invention are dissolved, After adding this to an excipient, a water independent or if needed, add alcohols and the sugars and the water-soluble binding material which perform a wet kneading granulation, and dry or are used for this invention are dissolved, After spraying on the excipient which made this flow and performing fluid bed granulation, the codissolution thing of sugars and a water-soluble binding material used for this invention is obtained by drying. Although this codissolution thing is uniformly distributed in a granulation thing in the state of a semi solid, the granulation surface is in dryness. It may add at which stage before tableting, and a granulation front stirrup compresses the mixture of the granulation thing or drug containing a drug, and a granulation thing by the low-pressure power of about 20 - about 300 kg/cm^2, and makes a porous tablet fabricate a drug. The obtained porous tablet is a tablet in which the intensity of what collapses promptly within the mouth is low, and this state is insufficient. However, a codissolution thing solidifies by warming at the temperature which allows this tablet to stand for several hours - several days at a room temperature, or exceeds a room temperature, and aging at a temperature higher than about 40 ** for several 10 seconds - for several days for for about 1 minute to about 24 hours lower [it is desirable and] than the softening temperature of a water-soluble binding material. Intensity becomes high, sufficient intensity for handling can be attained and the tablet solidified according to neglect conditions usual [these] or positive aging shows the character to collapse promptly within the mouth.
[0031]
[Example(s) and Function]Although working example and a comparative example are shown below and the focus which was excellent in the tablet of a tablet of this invention, a manufacturing method for the same, and this invention is shown, this invention is not limited to these working example. The measuring method of the solubility of the sugars etc. which are used for below by this invention is also indicated.
[0032]Working example 1:

[Table 1]

Ingredient	Weight	Weight %
- Sorbitol	4mg	2%
- polyvinyl-pyrrolidone	4mg	2%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	2.5%
- magnesium stearate	1 mg	
sum total	200mg	

[0033]4g of polyvinyl pyrrolidones (K30, BASF A.G. make) and 4 g of sorbitol (the Nacalai Tesque make, solubility about 130g) were mixed with the mortar, subsequently the water 10g was added, 15 g of ethanol was added further, and it was made to dissolve. What put optimum dose of mannitol (the Kao make, solubility about 18.5g) and 5 g of mosapride citrate into the plastic bag, and was mixed was moved to the mortar, and after adding and kneading the above-mentioned solution to this, it dried at 50 ** with the compartment dryer for 16 hours. Magnesium stearate was added after the particle size regulation by 24 mesh sieves, and it put into the plastic bag, mixed, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg at 8.0 mm in diameter with the single-engined tableting machine (2B type, made in the Kikusui factory). The obtained tablet was aged for three days at the room temperature, and a 200 mg [per dose] chewable tablet was obtained.

[0034]Working example 2: The same formula as working example 1 After tableting in the similar way indicated in working example 1 using [Table 1], it aged at 70 ** for 6 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0035]Working example 3:

[Table 2]

Ingredient	Weight	Weight %
- Xylitol	4.5mg	1.5%
- polyvinyl-pyrrolidone	4.5mg	1.5%
- mannitol (excipient)	Optimum dose	
- alacepril	12.5mg	4.2%
- ****- menthol	1 mg	
- magnesium stearate	1.5 mg	
sum total of 300 mg(s)		

[0036]A fluidized-bed-granulation device (flow coater: FLO-5 type, the Freund Industrial make) is used, 125g of alacepril and optimum dose of mannitol (the Kao make, solubility about 18.5g) are made to flow, 45g of polyvinyl pyrrolidones (K30, BASF A.G. make) and 45 g of xylitol (the Eisai make, solubility about 135g) which were dissolved in 1000 g of mixture of water-ethanol (1:1) were sprayed and corned, and it dried within the fluid bed succeedingly. 10g of ****- menthol and the magnesium stearate 15g are added after a particle size regulation with the twin rotor which attached 32 mesh screens, It mixed using the V shaped rotary mixer, was

considered as the granulation for tableting, and tableted to the with 9.5 mm in diameter, and a hardness of 0.5 kg tablet using the rotary tableting machine (the clean press C19, made in the Kikusui factory). The obtained tablet was aged for three days at the room temperature, and a 300 mg [per dose] chewable tablet was obtained.

[0037]Working example 4: The same formula as working example 3 After tableting in the similar way indicated in working example 3 using [Table 2], it aged at 70 ** for 3 hours, and a 300 mg [per dose] chewable tablet was obtained.

[0038]Working example 5:

[Table 3]

Ingredient	Weight	Weight %
- Xylitol	4.5mg	1.5%
- hydroxypropylcellulose	3mg	1%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5 mg	1.7%
- ****- menthol	1 mg	
- magnesium stearate	1.5 mg	
sum total	300 mg	

[0039]According to the formula of Table 3, 45 g of xylitol (the Eisai make, solubility of about 135g), 30 g of hydroxypropylcellulose (L, product made from a Japanese tub) was dissolved in 1500 g of mixture of water-ethanol (1:1), and it processed like working example 3, and tableted to the tablet with a hardness of 0.2 kg, aging for three days was further performed at the room temperature, and a 300 mg [per dose] chewable tablet was obtained.

[0040]Working example 6:

[Table 4]

Ingredient	Weight	Weight %
- Erythritol	6 mg	2%
- polyvinyl-pyrrolidone	9 mg	3%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5 mg	1.7%
- ****- menthol	1 mg	
- magnesium stearate	1.5 mg	
sum total	300 mg	

[0041]Polyvinyl pyrrolidone[PVP (K30, BASF A.G. make)] Mixed 90g and 60 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) within the beaker, and it was made to dissolve in the water 150g, and also 200 g of ethanol was added. Optimum dose of mannitol (the Kao make, solubility about 18.5g) and 50 g of mosapride citrate were mixed with the high-speed stirring granulator (vertical granulator:VG25, Powrex make), continuously, the above-mentioned PVP-erythritol solution was added and stirring granulation was carried out for 5 minutes. It granulated with the flash plate mill and dried with the core box air blasting dryer

for 16 hours. 10g of ****- menthol and the magnesium stearate 15g were added after the particle size regulation by 24 mesh sieves after desiccation, and it mixed using the V shaped rotary mixer, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg using the rotary tableting machine (the clean press C19, made in the Kikusui factory). The obtained tablet was aged at 50 ** for 12 hours, and a 300 mg [per dose] chewable tablet was obtained.

[0042]Working example 7:

[Table 5]

Ingredient	Weight	Weight %
- Glucose	9 mg	3%
- pullulan	1.5mg	0.5%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5 mg	1.7%
- ****- menthol	1 mg	
- magnesium stearate	1.5 mg	
sum total 300 mg		

[0043]According to the formula of Table 5, 90g of glucose (the Wako Pure Chem make, solubility about 75g) and 15 g of pullulan (PI-20, made in Hayashibara) are dissolved in the water 150g, It processed like working example 6, and tableted to the tablet with a hardness of 0.3 kg, aging of 3 hours was performed at 70 more **, and a 300 mg [per dose] chewable tablet was obtained.

[0044]Working example 8:

[Table 6]

Ingredient	Weight	Weight %
- Erythritol	3 mg	1%
- hydroxypropylmethylcellulose	3 mg	1%
- erythritol (excipient)	Optimum dose	
- mosapride citrate	5 mg	1.7%
- magnesium stearate	1.5 mg	
sum total	300 mg	

[0045]The formula of Table 6 is followed and it is hydroxypropylmethylcellulose. [HPMC (TC-5R, product made from the Shin-etsu chemicals)] After having dissolved 30g and 30 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) in the water 150g, adding 200 g of ethanol further and making it dissolve, it processed like working example 6 and tableted to the tablet with a hardness of 0.3 kg. Aging of 3 hours was performed for the obtained tablet at 70 **, and a 300 mg [per dose] chewable tablet was obtained.

[0046]Working example 9:

[Table 7]

Ingredient	Weight	Weight %
- Erythritol	6mg	2%
- polyvinyl-pyrrolidone	15mg	5%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	1.7%
- ****- menthol	1mg	
- magnesium stearate	3 mg	
sum total	300mg	

[0047]According to the formula of Table 7, 60 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) and 150 g of polyvinyl pyrrolidones (K30, BASF A.G. make) were dissolved in 2000 g of mixture of water-ethanol (1:1), and it processed like working example 3, and tableted to the tablet with a hardness of 0.3 kg. Aging of 4 hours was performed for the obtained tablet at 70 **, and a 300 mg [per dose] chewable tablet was obtained.

[0048]Working example 10:

[Table 8]

Ingredient	Weight	Weight %
- Shook sirloin	6mg	2%
- polyvinyl-pyrrolidone	6mg	2%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	1.7%
- ****- menthol	1mg	
- magnesium stearate	3 mg	
sum total	300mg	

[0049]According to the formula of Table 8, 60 g of shook sirloins (the product made from great Japan Meiji Sugar Manufacturing, solubility about 170g) and 60 g of polyvinyl pyrrolidones (K30, BASF A.G. make) were dissolved in 1500 g of mixture of water-ethanol (1:1), and it processed like working example 3, and tableted to the tablet with a hardness of 0.3 kg. Aging of 4 hours was performed for the obtained tablet at 70 **, and a 300 mg [per dose] chewable tablet was obtained.

[0050]Working example 11:

[Table 9]

Ingredient	Weight	Weight %
- Erythritol	6mg	2%
- polyvinyl-pyrrolidone	6mg	2%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	1.7%
- ****- menthol	1mg	
- magnesium stearate	3 mg	

sum total	300mg

[0051]According to the formula of Table 9, 60 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) and 60 g of polyvinyl pyrrolidones (K30, BASF A.G. make) were dissolved in 2000 g of mixture of water-ethanol (1:1), and it processed like working example 3, and tableted to the tablet with a hardness of 0.3 kg. Aging for 2 minutes was performed for the obtained tablet at 80 **, and a 300 mg [per dose] chewable tablet was obtained.

[0052]Working example 12:

[Table 10]

Ingredient	Weight	Weight %
- Erythritol	30mg	10%
- polyvinyl-pyrrolidone	6mg	2%
- mannitol (excipient)	Optimum dose	
- berberine tannate	30mg	10%
- ****- menthol	1mg	
- magnesium stearate	3 mg	
sum total	300mg	

[0053]According to the formula of Table 10, 300 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) and 60 g of polyvinyl pyrrolidones (K30, BASF A.G. make) were dissolved in 1500 g of mixture of water-ethanol (1:1), and it processed like working example 3, and tableted to the tablet with a hardness of 0.5 kg. Aging of 4 hours was performed for the obtained tablet at 70 **, and a 300 mg [per dose] chewable tablet was obtained.

[0054]Working example 13:

[Table 11]

Ingredient	Weight	Weight %
- Shook sirloin	2 mg	1%
- polyvinyl-pyrrolidone	4 mg	2%
- water-soluble gelatin	2 mg	1%
- mannitol (excipient)	Optimum dose	
- brotizolam	0.25 mg	0.13%
- ****- menthol	1 mg	
- magnesium stearate	2 mg	
sum total	200 mg	

[0055]According to the formula of Table 11, except for dissolving brotizolam in granulation liquid with a binding material, it processed like working example 3, and tableted to the tablet with a hardness of 0.1 kg at tableting preassure 120kg/cm^2 and 9.0 mm in diameter. Aging for 5 minutes was performed for the obtained tablet at 70 **, and a 200 mg [per dose] chewable tablet was obtained.

[0056]Working example 14:

[Table 12]

Ingredient	Weight	Weight %
- Shook sirloin	1.8 mg	1%
- polyvinyl-pyrrolidone	3.6 mg	2%
- noy silyne	5 mg	1%
- mannitol (excipient)	optimum dose,	
- erythritol (excipient)	36 mg	
- Aspara Teemu	0.9 mg	
- loperamide hydrochloride	0.25 mg	0.14%
- berberine tannate	37.5 mg	
- magnesium stearate	2 mg	
sum total	180 mg	

[0057]It processed like working example 3, according to the formula of Table 12, after tableting a tablet in 8.5 mm in diameter, and hardness of 0.2 kg, it aged for 5 minutes at 70 **, and a 180 mg [per dose] chewable tablet was obtained.

[0058]Comparative-example 1: The conditions by which a process (a) is not fulfilled

[Table 13]

Ingredient	Weight	Weight %
- Erythritol	4mg	2%
- polyvinyl-pyrrolidone	4mg	2%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5-mg	2.5%
- magnesium stearate	1 mg	
sum total	200mg	

[0059]Polyvinyl pyrrolidone[PVP (K30, BASF A.G. make)] 40 g was dissolved in the water 10g and the mixture of 15 g of ethanol. optimum dose of mannitol (the Kao make, solubility of about 18.5g) on the other hand, and erythritol (the Nikken Chemicals make.) Solubility About 47.5g 40g and 50 g of mosapride citrate were put into the plastic bag, and it mixed, and it moved to the mortar, the above-mentioned PVP-ethanol solution was added, and it kneaded with the pestle, and dried at 50 ** with the core box air blasting dryer for 16 hours. The magnesium stearate 10g was added after the particle size regulation by 24 mesh sieves, and it mixed with the plastic bag, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg using the single-engined tableting machine (2B type, made in the Kikusui factory). The tablet furthermore obtained was aged for three days at the room temperature, and a 200 mg [per dose] chewable tablet was obtained.

[0060]Comparative-example 2: It tableted to the tablet with a hardness of 0.5 kg using the single-engined tableting machine (2B type, made in the Kikusui factory) using the granulation for tableting obtained by the condition comparative example 1 by which a process (a) is not fulfilled. The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable

tablet was obtained.

[0061]Comparative-example 3: The conditions by which a process (a) is not fulfilled[0062]It carried out using the same formula as Table 13 in the comparative example 1. That is, 40 g of erythritol (Nikken Chemicals make: solubility about 47.5g) was dissolved in the water 10g and 15 g of ethanol. Optimum dose of mannitol (the Kao make, solubility about 18.5g) and polyvinyl pyrrolidones on the other hand [PVP (K30, BASF A.G. make)] 40g and 50 g of mosapride citrate were put into the plastic bag, and it mixed, and it moved to the mortar, the above-mentioned erythritol ethanol solution was added, and it kneaded with the pestle, and dried at 50 ** with the core box air blasting dryer for 16 hours. The magnesium stearate 10g was added after the particle size regulation by 24 mesh sieves, and it put into the plastic bag, mixed, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg using the single-engined tableting machine (2B type, made in the Kikusui factory). The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0063]Comparative-example 4: It tableted to the tablet with a hardness of 3.0 kg using the single-engined tableting machine (2B type, made in the Kikusui factory) using the granulation for tableting obtained by the condition comparative example 3 by which a process (a) is not fulfilled. The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0064]Comparative-example 5: The formula with unsuitable sugars used at a process (a)

[Table 14]

Ingredient	Weight	Weight %
- Lactose	4mg	2%
- polyvinyl-pyrrolidone	4mg	2%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	2.5%
- magnesium stearate	1 mg	
sum total	200mg	

[0065]Polyvinyl pyrrolidone[PVP (K30, BASF A.G. make)] 40g and 40 g of lactose (the product made by DMV, solubility about 13.5g) were dissolved in the water 10g and 15 g of ethanol. On the other hand, optimum dose of mannitol (the Kao make, solubility about 18.5g) and 50 g of mosapride citrate were put into the plastic bag, and it mixed, and it moved to the mortar, the above-mentioned PVP-lactose solution was added, and it kneaded with the pestle, and dried at 50 ** with the core box air blasting dryer for 16 hours. The magnesium stearate 10g was added after the particle size regulation by 24 mesh sieves, and it put into the plastic bag, mixed, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg using the single-engined tableting machine (2B type, made in the Kikusui factory). The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0066]Comparative-example 6: The formula with unsuitable sugars used at a process (a)

[Table 15]

Ingredient	Weight	Weight %
- Mannitol	4mg	2%
- polyvinyl-pyrrolidone	4mg	2%
- erythritol (excipient)	Optimum dose	
- mosapride citrate	5mg	2.5%
- magnesium stearate	1 mg	
sum total	200mg	

[0067]Polyvinyl pyrrolidone[PVP (K30, BASF A.G. make)] 40g and 40 g of mannitol (the Kao make, solubility about 18.5g) were dissolved in the water 10g and 15 g of ethanol. On the other hand, optimum dose of erythritol (the Nikken Chemicals make, solubility about 47.5g) and 50 g of mosapride citrate were put into the plastic bag, and it mixed, and it moved to the mortar, the above-mentioned PVP-mannitol solution was added, and it kneaded with the pestle, and dried at 50 ** with the core box air blasting dryer for 16 hours. The magnesium stearate 10g was added after the particle size regulation by 24 mesh sieves, and it mixed with the plastic bag, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 3.0 kg using the single-engined tableting machine (2B type, made in the Kikusui factory). The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0068]Comparative-example 7: The formula with a water-soluble unsuitable binding material [Table 16]

Ingredient	Weight	Weight %
- Erythritol	4mg	2%
- cornstarch	3mg	1.5%
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5mg	2.5%
- magnesium stearate	1 mg	
sum total	200mg	

[0069]After having stirred for 15 minutes at 80 **, having prepared the starch paste, after distributing 30 g of cornstarch (made by Japan Maize Products) within a water 30g beaker, and dissolving 40 g of erythritol (the Nikken Chemicals make, solubility about 47.5g) in this, temperature was lowered to 30 **. On the other hand, optimum dose of mannitol (the Kao make, solubility about 18.5g) and 50 g of mosapride citrate were put into the plastic bag, and it mixed, and it moved to the mortar, the above-mentioned erythritol starch paste solution was added, and it kneaded with the pestle, and dried at 50 ** with the core box air blasting dryer for 16 hours. The magnesium stearate 10g was added after the particle size regulation by 24 mesh sieves, and it put into the plastic bag, it mixed, was considered as the granulation for tableting, and tableted to the tablet with a hardness of 0.5 kg using the single-engined tableting machine (2B type, made in the Kikusui factory). The obtained tablet was aged at 70 ** for 3 hours, and a 200 mg [per dose] chewable tablet was obtained.

[0070]Comparative-example 8: The conditions which do not perform desiccation in a process (b)

[Table 17]

Ingredient	Weight	Weight %.
- Erythritol	9mg	3%,
- polyvinyl-pyrrolidone	6mg	2%,
- mannitol (excipient)	Optimum dose	
- mosapride citrate	5-mg	1.7%
- and magnesium stearate	3 mg.	
sum total	300mg	

[0071]9g of erythritol (the Nikken Chemicals make, solubility about 47.5g), and a polyvinyl pyrrolidone [PVP (K30, BASF A.G. make)] 6 g was dissolved in the water 10g, and 15 g of ethanol was added further. Optimum dose of mannitol (the Kao make, solubility about 18.5g) and 5 g of mosapride citrate were put into the plastic bag, it mixed, this was moved to the mortar, the above-mentioned erythritol PVP solution was added further, and it kneaded with the pestle. Although tableting was tried with the single-engined tableting machine (2B type, made in the Kikusui factory), the kneaded object adhered to the pestle and the continuation tableting was not able to do the kneaded object with which this surface became wet.

[0072]The decay time in the mouth and hardness of the tablet of working example 1-14 and the tablet of the comparative examples 1-8 are shown in Table 18 and 19, respectively. The tablet whose decay time is less than 30 seconds estimated that the purpose of this invention was attained by the conditions which hardness shows to the footnote of not less than 2.5 kg and the following table in the following hardness and the experiment of collapsibility.

[0073]

[Table 18]

試験項目	実施例1	実施例2	実施例3	実施例4
崩壊時間*1 硬度	18秒 2.7 kg	20秒 2.9 kg	20秒 2.7 kg	20秒 3.0 kg
試験項目	実施例5	実施例6	実施例7	実施例8
崩壊時間*1 硬度	25秒 2.8 kg	20秒 2.9 kg	25秒 3.0 kg	20秒 2.8 kg
試験項目	実施例9	実施例10	実施例11	実施例12
崩壊時間*1 硬度	25秒 4.0 kg	20秒 2.7 kg	15秒 2.5 kg	28秒 2.6 kg
試験項目	実施例13	実施例14		
崩壊時間*1 硬度	18秒 4.6 kg	28秒 4.0 kg		

*1 decay time : time after the tongue has described lightly, without choosing five healthy adult men as a panelist, and blowing a tablet within the mouth, until a tablet collapses[0074]

[Table 19]

試験項目	比較例1	比較例2	比較例3	比較例4
崩壊時間*1 硬度	12秒 0.7 kg	15秒 1.2 kg	15秒 0.6 kg	〉60 秒 3.0 kg
試験項目	比較例5	比較例6	比較例7	比較例8
崩壊時間*1 硬度	25秒 1.0 kg	60秒 3.2 kg	50秒 1.0 kg	—*2 —*2

*1 decay time : time after the tongue has described lightly, without choosing five healthy adult men as a panelist, and blowing a tablet within the mouth, until a tablet collapses.

*2 -- a kneaded object adheres to a pestle and tableting is impossible -- un-measuring.

Underline problem part.

[0075]As shown in above-mentioned Table 18 and 19, the tablet of working example 1-14 showed the value with which it can be satisfied of decay time and hardness, but decay time and hardness had a problem, as for a tablet of other comparative examples, there was a problem in either decay time and hardness, and, as for the tablet of the comparative example 7, it was unsuitable.

[0076]Put 20 ml of 25 ** purified water into the measurement beaker of the solubility of sugars, and various sugars are added, stirring, It added xylitol, sorbitol, glucose, and 1g of shook sirloins at a time, erythritol added 0.5g of lactose and mannitol at a time, and quantity which is stirred for 1 hour and dissolved was made into the solubility of the sugars in this Description. [0.1g of]

[0077]

[Effect of the Invention]As explained above, the manufacturing method of this invention can be performed without using special equipment, and the target chewable tablet can be manufactured simple in large quantities. The tablet manufactured by the method of this invention shows good collapsibility within the mouth, and its intensity is enough, and it is an outstanding chewable tablet which does not collapse during handling.